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Effect of Efavirenz on the Pharmacokinetics of Ethinyl Estradiol and Norgestimate in Healthy Female Subjects

Jenny Zhang
Bristol-Myers Squibb
Princeton, NJ 08534
Phone: 609-818-6512
E-mail: jenny.zhang1@bms.com

H. Sevinsky, T. Eley, B. He, A. Persson, D. Garner, C. Yones, R. Nettles, R. Bertz and **J. Zhang**
Bristol-Myers Squibb Research and Development, Princeton, NJ USA

Introduction

- Efavirenz (EFV) is a nonnucleoside reverse transcriptase inhibitor (NNRTI) that is used in the treatment of HIV-1 infection. It is an inducer of CYP3A4 and uridine-diphosphate glucuronosyl transferases (UGTs) in vivo.[1,2,3] EFV is a Pregnancy Category D drug. Preventing pregnancy is critical in women receiving EFV as part of their antiretroviral therapy
- Oral contraceptives (OC) containing an estrogen (ethinyl estradiol, EE) and a progestin are among the most frequently used methods of birth control
- In a previous study, EFV 400 mg increased the single dose EE Cmax and AUC by 5% and 37%, respectively
- EE is metabolized by sulfotransferases (SULTs), CYP3A4 and UGTs.[4] The specific enzymes involved in progestin metabolism have not been well-defined; however CYP3A4 and UGTs may play a role.[5,6] Exposure to OC components could potentially be impacted when coadministered with EFV
- The US Prescribing Information for Sustiva includes the following information and recommendation: The potential interaction of EFV with OCs has not been fully characterized. A reliable method of barrier contraception should be used in addition to oral contraceptives
- Progesterone is an endogenous hormone that peaks 5 - 9 days after ovulation; in women taking OCs, ovulation is suppressed and progesterone levels typically remain below 150 ng/dL
- This study was conducted in order to provide a better understanding of the interaction between EFV and the components of OCs

Objectives

Primary:

- To determine the effect of coadministration of EFV 600 mg on the pharmacokinetics (PK) of EE and norelgestromin (NGMN), an active metabolite of the progestin norgestimate (NGM)

Secondary:

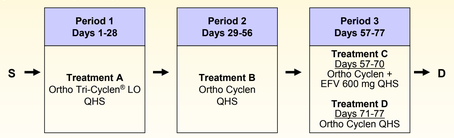
- To characterize the PK of EFV when coadministered with the OC Ortho Cyclen®
- To assess the effect of EFV coadministered with Ortho Cyclen on serum progesterone levels
- To assess the safety of EFV coadministered with Ortho Cyclen
- An exploratory analysis of the PK of levonorgestrel (LNG), an active metabolite of NGMN and an active component of some OCs, was conducted in a subset of 6 subjects

Methods

Study Design

- Open-label, 3-period, 4-treatment single sequence study in healthy female subjects who had been receiving a stable regimen of OC for at least 2 months

Figure 1. Study Design



S = Screening, D = Discharge

Ortho Tri-Cyclen LO: Phase I = 0.025 mg EE + 0.18 mg NGM, Phase II = 0.025 mg EE + 0.215 mg NGM, Phase III = 0.025 mg EE + 0.25 mg NGM

Ortho Cyclen: 0.025 mg EE + 0.25 mg NGM

- Follow up visits were conducted on Day 85 ± 2 days and Day 108 ± 2 days for pregnancy testing and adverse event (AE) follow up.

Methods (continued)

Pharmacokinetics

- Serial blood samples were collected up to 24 hours post-dose on Days 14, 42 and 70 for EE PK analysis, Days 42 and 70 for NGMN PK analysis and on Day 70 for EFV PK analysis
  - Non-compartmental analysis using the validated program Kinetica™:
- EE, NGMN and EFV Cmax, Tmax, AUC(TAU) and Cmin (concentration 24 hours post-dose) for all subjects
  - Plasma samples assayed via LC-MS/MS:
  - EE: standard curve from 10 - 500 pg/mL, QC deviations within ± 1.6%
  - NGMN: standard curve from 99.5 - 4975 pg/mL, QC deviations within ± 2.5%
  - EFV: standard curve from 10 - 10,000 ng/mL, QC deviations within ± 11.2%
  - LNG: standard curve from 100 - 10,000 pg/mL, QC deviations within ± 0.5%

Pharmacodynamics

- Serum progesterone levels were determined at Day -2 and during each treatment (Study Day 18, 46 and 74) as a biomarker for possible ovulation

Statistics

- The effect of EFV on the PK of EE, NGMN and LNG were assessed by point estimates and 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) for EE, NGMN, and LNG Cmax, AUC(TAU) and Cmin, derived using general linear models on log-transformed data
- Differences in endogenous progesterone levels between treatments and their corresponding 95% CIs were estimated. These estimates were constructed using general linear models

Results

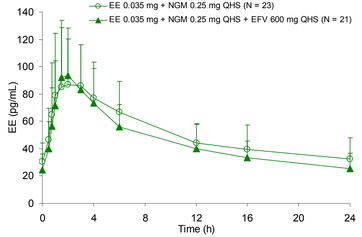
Demographics

- 28 women were enrolled and treated, 19 subjects completed the study
- 9 subjects discontinued:
  - 2 due to poor adherence, 1 due to positive drug screen, 5 withdrew consent
- Mean age (range): 28 years (18 - 42 years)
- Mean BMI: 25.4 kg/m^2
- 68% were White, 21% were Black, 4% were native Hawaiian/Pacific Islander and 7% were "other"

Pharmacokinetics

Ethinyl Estradiol

Figure 2. Mean (SD) plasma concentration versus time profiles for EE



Note: mean profile for Treatment A (Ortho Tri-Cyclen LO) is not shown

Results (Cont'd)

Table 1. Statistical Analyses for EE PK Parameters

PK Parameter	Adjusted Geometric Means — Treatment (EE Dose): Ortho Tri-Cyclen LO (0.025 mg) N = 28	Ortho Cyclen (0.035 mg) N = 23	Ortho Cyclen + EFV (0.035 mg) N = 21	GMR (90% CI): Ortho Cyclen + EFV / Ortho Cyclen	Ortho Cyclen + EFV / Ortho Tri-Cyclen LO*
Cmax (pg/mL)	65.4	96.2	102	**1.06 (0.95, 1.19)**	1.56 (1.39, 1.76)
AUC(TAU) (pg•h/mL)	756	1150	1037	**0.90 (0.80, 1.01)**	1.37 (1.21, 1.55)
Cmin (pg/mL)	16.6	25.3	23.3	**0.92 (0.75, 1.14)**	1.40 (1.15, 1.71)

GMR = geometric mean ratio
* comparisons are 0.035 mg EE + EFV relative to 0.025 mg EE in the absence of EFV

- EFV does not impact EE exposures when co-administered with Ortho Cyclen

Progestins

Figure 3. Mean Plasma Concentration versus Time Profiles for NGMN

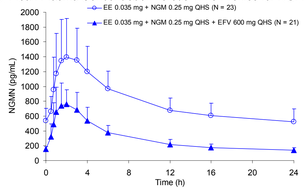
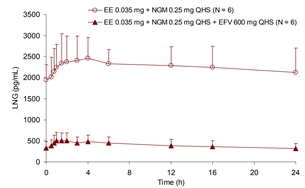


Table 2. Statistical Analyses for NGMN PK Parameters

PK Parameter	Adjusted Geometric Means — Treatment: Ortho Cyclen N = 23	Ortho Cyclen + EFV N = 21	GMR (90% CI): Ortho Cyclen + EFV / Ortho Cyclen
Cmax (pg/mL)	1645	883	**0.54 (0.48, 0.61)**
AUC(TAU) (pg•h/mL)	18328	6522	**0.36 (0.33, 0.38)**
Cmin (pg/mL)	500	90	**0.18 (0.15, 0.21)**

GMR = geometric mean ratio

Figure 4. Mean Plasma Concentration versus Time Profiles for LNG



Results (Cont'd)

Table 3. Statistical Analyses for LNG PK Parameters

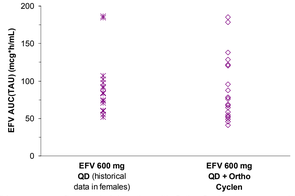
PK Parameter	Adjusted Geometric Means — Treatment: Ortho Cyclen N = 6	Ortho Cyclen + EFV N = 6	GMR (90% CI): Ortho Cyclen + EFV / Ortho Cyclen
Cmax (pg/mL)	2618	510	**0.20 (0.17, 0.23)**
AUC(TAU) (pg•h/mL)	53375	8811	**0.17 (0.13, 0.21)**
Cmin (pg/mL)	2061	289	**0.14 (0.10, 0.20)**

GMR = geometric mean ratio
B = Ortho Cyclen, C = Ortho Cyclen + EFV 600 mg

- NGMN and LNG exposures were markedly decreased in the presence of EFV

Efavirenz

Figure 5. Scatter Plot of EFV AUC(TAU): Administered Alone in Women (historical data) and Coadministered with Ortho Cyclen



- EFV exposures after coadministration with Ortho Cyclen are comparable to EFV administered alone in healthy females

Pharmacodynamics

Table 4. Statistical Analyses for Progesterone Levels

Treatment	Adjusted Mean (ng/dL)	Difference	Difference in Adjusted Means Point Estimates (90% CI)
A: Ortho Tri-Cyclen LO	38.9	D - A	4.0 (-2.5, 10.6)
B: Ortho Cyclen	39.9	D - B	3.0 (-5.5, 11.5)
D: Ortho Cyclen (3 days after EFV coad.)	42.9	---	---

A = Ortho Tri-Cyclen LO (day 18), B = Ortho Cyclen (day 46), D = Ortho Cyclen (day 74, 3 days after completing Ortho Cyclen + EFV)

- Single time point progesterone levels after coadministration of Ortho Cyclen and EFV 600 mg are similar to those after administration of Ortho Cyclen alone.
- All subjects' progesterone levels collected at a single time point during 1 cycle on EFV + Ortho-Cyclen were less than 125 ng/dL, below the 1000 ng/dL indicative of ovulation

Results (Cont'd)

Safety

Table 5. Safety Results

	Treatment: Ortho Tri-Cyclen LO	Ortho Cyclen	Ortho Cyclen + EFV	Ortho Cyclen
# Subjects	28	25	22	21
Total # AEs (Grades 1-4)	46	22	157	31
Subjects with AEs - N (%)	20 (71.4%)	15 (60%)	22 (100%)	13 (61.9%)
Most Frequent AEs - N(%) of subjects				
metrorrhagia (Grade 1)	10 (35.7%)	4 (16.0%)	5 (22.7%)	3 (14.3%)
headache (Grades 1-3)	6 (21.4%)	5 (20.0%)	6 (27.3%)	3 (14.3%)

AEs: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = very severe

- One (1) SAE of suicide attempt was reported during the post-treatment follow-up period, considered probably related to study drug. Subject had a history of prior psychiatric hospitalization and medication for depression, not disclosed at screening
- Most AEs were mild to moderate in intensity. Three (3) severe AEs in 3 subjects (headache, anhedonia and severe depressed mood) were reported and considered probably related to study drug
- One (1) subject had AST and ALT laboratory abnormalities that were AEs and considered not related to study treatment

Discussion

- In a previous study that resulted in increased single dose EE exposures when administered with EFV 400 mg, EFV was administered for only 7 days. The ability of EFV to induce CYP3A4 may not have been fully observed
- In the current study, EFV 600 mg was dosed for 14 days with no observed impact on EE PK. The effect of EFV on EE PK potentially involves inhibition/induction of multiple metabolic pathways, resulting in no net change in EE exposure
- Decreases in NGMN and LNG exposures are potentially due to induction of CYP3A4 and/or UGTs by EFV
- Progesterone levels remained suppressed (<10 ng/mL) when EFV was coadministered with OCs; however these levels were assessed at a single time point within the cycle and should be interpreted with caution

Conclusions

- EFV does not alter EE exposure when coadministered with Ortho Cyclen
- EFV significantly reduces exposure to NGMN and LNG when coadministered with Ortho Cyclen
- EFV exposures after coadministration of Ortho Cyclen with EFV are comparable to historical data in women when EFV 600 mg is administered alone
- AEs reported with Ortho Cyclen + EFV are not unexpected and consistent with those previously reported for both treatments
- These results reinforce the need for reliable methods of barrier contraception when taking OCs with EFV

References

1. Sustiva® (efavirenz) capsule and tablets. US prescribing information. Bristol-Myers Squibb Co., Princeton, NJ 2008.
2. Isentress™ (raltegravir) tablets. US prescribing information. Merck and Co., Inc. Whitehouse Station, NJ, 2008.
3. Noxafil® (posaconazole) oral suspension. US prescribing information. Schering-Plough, Kenilworth, NJ, 2008.
4. Doose DR, Wang SS, Padmanabhan M, et al. Epilepsia 2003; 44(4): 540 - 549.
5. Hammomd GL, Abrams LS, Creasy GW, et al. Contraception 2003; 67(2): 93 - 99.
6. Kuhn W, Blode H and Mahler M. Contraception 1994; 49: 225 - 263.

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